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Transseptal or retrograde approach for transcatheter ablation of left sided

accessory pathways: a systematic review and meta-analysis

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transaortic access

28 **Abstract**

29 **Background.** Transcatheter ablation is the most effective treatment for patients with symptomatic
30 or high-risk accessory pathways (AP). At present, no clear recommendations have been issued on
31 the optimal approach for left sided AP ablation. We performed this meta-analysis to compare the
32 safety and efficacy of transaortic retrograde versus transseptal approach for left sided AP ablation.

33 **Methods and Results.** MEDLINE/PubMed and Cochrane database were searched for pertinent
34 articles from 1990 until 2016. Following inclusion/exclusion criteria application, 29 studies were
35 selected including 2030 patients (1013 retrograde, 1017 transseptal) from 28 observational single
36 Centre studies and one randomized trial. Patients approached by transseptal puncture presented a
37 significantly higher acute success (98% vs. 94%, $p=0.040$). The incidence of late recurrences
38 ($p=0.381$) and complications ($p=0.301$) did not differ among the two groups, but the pattern of
39 complications differed: vascular complications were more frequent with transaortic retrograde
40 approach, while cardiac tamponade was the main transseptal complication. No difference was noted
41 in terms of procedural duration and fluoroscopy time ($p=0.230$ and $p=0.980$, respectively). Meta-
42 regression analysis showed no relation between year of publication and acute success ($p=0.325$) or
43 incidence of complications ($p=0.795$); additionally, no direct relation was found between age and
44 acute success ($p=0.256$) or complications ($p=0.863$).

45 **Conclusions.** Left sided AP transcatheter ablation is effective in around 95% of the cases, with a
46 very limited incidence of complications. Transseptal access provides higher acute success in
47 achieving AP ablation; late recurrences are rare but observed similarly following both approaches.
48 Retrograde approach is affected by a relatively high incidence of vascular complications.

49 Abstract word count: 250

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52 **Introduction**

53 Wolff-Parkinson-White syndrome is characterized by the concomitant presence of cardiac pre-
54 excitation and arrhythmias as atrio-ventricular re-entrant tachycardia or atrial fibrillation (AF). Less
55 than 1% of patients with cardiac pre-excitation may present a significant risk of sudden cardiac
56 death, due to very high conduction properties of the atrioventricular accessory pathway (AP) [1].
57 Treatment is warranted to prevent this risk of sudden death in high-risk asymptomatic patients, or to
58 prevent re-entrant tachycardias in symptomatic patients [2,3].

59 The APs can be situated everywhere in the tricuspid or mitral annuli, with the exception of the
60 mitral-aortic continuity. Transcatheter ablation of the AP is the most effective treatment for patients
61 affected by Wolff-Parkinson-White syndrome and for high-risk asymptomatic pre-excitation. The
62 most recent guidelines recommend transcatheter ablation as first-line treatment for these patients
63 [2], due to its high efficacy and safety in experienced Centres.

64 Bearing in mind the different possible localizations, right APs can be approached for ablation from
65 the femoral or subclavian veins, while left sided APs can be approached by transaortic retrograde
66 pathway or transseptal puncture. These two approaches differ in terms of technique, materials,
67 potential complications and easy access to the AP, and are usually chosen alternatively according to
68 the operators' comfort level and preference. However, no clear recommendation has been proposed
69 on the ideal approach for transcatheter ablation of left sided APs. In particular, common practice is
70 mainly based on single-Centre, observational studies, and no large randomized trials or registries
71 have been published.

72 We therefore performed this systematic review and meta-analysis including randomized and
73 observational studies comparing the outcome of transaortic retrograde versus transseptal approach,
74 aiming to assess the optimal approach for left sided AP transcatheter ablation, in terms of both
75 safety and efficacy.

76 **Materials and Methods**

77 *Search strategy and studies selection*

78 The present study was conducted in accordance with current guidelines, including the recent
79 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [4] amendment to
80 the Quality of Reporting of Meta-analyses (QUOROM) statement, as well as recommendations
81 from The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology
82 (MOOSE) [5]. All subjects included in the studies gave informed consent.

83 MEDLINE/PubMed and Cochrane database were searched for pertinent articles published in
84 English from 1990 until December 2016. The following terms: (“Left accessory pathway” OR “left
85 Wolff Parkinson White”) AND “catheter ablation” AND “radiofrequency” were used. Retrieved
86 citations were screened through abstract reading independently by two reviewers (M.M. and A.S.),
87 and divergences resolved after consensus. If the citations were deemed potentially pertinent, they
88 were then appraised as complete full-text reports according to the following explicit selection
89 criteria: (i) human observational or randomized studies, (ii) published in English between 1990 and
90 2016, (iii) investigating patients with left accessory pathways, (iv) including any duration of follow-
91 up. Exclusion criteria were (one enough for exclusion): (i) non-human setting, (ii) duplicate
92 reporting (in which case the manuscript reporting the largest sample of patients was selected), (iii)
93 case reports or papers including less than 10 patients; (iv) surgical AP ablation. Data concerning
94 study design and year of publication, population characteristics, intervention, complications, acute
95 and mid- or long-term outcome were extracted by two Authors and reviewed independently by a
96 third one (M.A.), being inserted in a single study database.

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100 *Statistical analysis*

101 Since most of the included studies had an observational design, meta-analysis and meta-regressions
102 were performed using random effect models. Primary outcomes of this systematic review were:
103 proportions of initial success (calculated as the ratio between successful procedures and number of
104 patients or as the ratio between successfully ablated pathways and the total number of treated
105 pathways), proportion of recurrences after a mid-term follow-up and proportion of complications.
106 Secondary outcomes were: total procedural time, fluoroscopy time (excluding those studies
107 characterized by a “zero-fluoroscopy” approach) and number of energy applications per procedure.
108 Meta-analysis of proportions was performed using STATA command “metaprop” [6], while meta-
109 analysis of continuous variables was performed using STATA command “metan” [7]. Aiming to
110 assess the impact of the type of procedural access (retrograde aortic vs transseptal), subgroup meta-
111 analysis was performed for both primary and secondary outcomes and a Q test for heterogeneity
112 between subgroups was computed. In addition, aiming to reduce the impact of potential biases
113 derived from patients’ characteristics or year of publication, using the primary outcomes as
114 dependent variables, pre-specified meta-regression analysis was performed through STATA
115 command “metareg” [8] to test whether interactions with (i) year when the study was published and
116 (ii) mean age of study participants were present.

117 Continuous variables were reported as mean (standard deviation) and categorical variables as counts
118 (percentage). Statistical analysis was performed using STATA version 12.0 (StataCorp, College
119 Station, TX, USA), considering p values < 0.05 statistically significant.

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124 **Results**

125 ***Search Results***

126 The search identified 269 abstracts referring to transcatheter ablation of left sided APs; among this
127 group, 233 were excluded following application of the inclusion and exclusion criteria; 36 of them
128 were selected and full text was read by two Authors; 7 were excluded because reporting repeated
129 data. Twenty-nine studies were finally included meeting all the pre-specified inclusion criteria. All
130 included articles were single-Centre studies; overall 28 observational studies and one randomized
131 trial were included. Complete details of the study flow-chart are described in in the Supplementary
132 Material, Supplementary Figure 1.

133 First Author, study design, publication date and complete main characteristics of each included
134 study are reported in the Supplementary Material, Supplementary Table 1 [9-37].

135 Overall, 2030 patients have been included in the analysis, 1013 approached by retrograde
136 transaortic access and 1017 by transseptal puncture. Baseline characteristics of the included
137 population in both groups are described in Table 1. Briefly, population included mainly young
138 adults, two thirds of whom were males. The most common location for left sided AP was left
139 lateral, followed by left posterior.

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141 ***Efficacy and safety endpoints***

142 As shown in Figure 1, patients approached by transseptal puncture presented a significantly higher
143 acute success of the ablation (98% vs. 94%, $p=0.040$) compared to transaortic retrograde approach.
144 Conversely, the incidence of late recurrences of cardiac pre-excitation did not differ significantly
145 among the two groups (3% vs. 2%, $p=0.381$; Figure 2). Concerning safety, the incidence of overall
146 complications was equally low in both groups (0.4% vs. 1.2%, $p=0.301$; Figure 2). Of note,
147 complications pattern was different: vascular complications (hematoma, pseudoaneurysm, aortic

148 regurgitation and coronary damage) were more frequent with transaortic retrograde approach, while
149 cardiac tamponade was the main complication of transseptal approach. Detailed complications are
150 reported in the Table 2.

151 Additionally, procedural duration and fluoroscopy time were investigated, and no difference was
152 noted between the two groups ($p=0.230$ and $p=0.980$, respectively; Figure 2).

153 Aiming to assess the impact of the currently available knowledge and technologies employed for
154 transcatheter ablation on the outcome and complications of the procedure, a meta-regression
155 analysis was performed to assess the impact of year of publication, showing no relation between
156 year of publication and acute success ($p=0.325$) or incidence of complications ($p=0.795$).

157 Additionally, due to the wide age range of the included patients, varying from children to middle
158 age, a meta-regression analysis was performed to assess the impact of age (Supplementary Figure
159 2), showing no direct relation with acute success ($p=0.256$) or complications ($p=0.863$).

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170 **Discussion**

171 The present meta-analysis, although mainly based on single high-volume Centres, observational
172 studies, includes the largest series of patients comparing the outcome of left sided AP transcatheter
173 ablation approaching alternatively by transseptal or retrograde transaortic access. This series
174 emerges due to the absence of large randomized trials or prospective registries assessing the
175 comparison between the two approaches for left sided AP ablation, resulting a potentially useful
176 tool to help Electrophysiologists in planning the access for left sided APs catheter ablation
177 procedures.

178 Overall, transseptal approach reported a higher acute success compared to transaortic retrograde
179 approach. In fact, in experienced Centres transseptal approach may lead to easier manoeuvrability
180 of the ablation catheters in the left atrium, compared to the more challenging manipulation
181 approaching from the left ventricle across the aortic arch. Additionally, a more direct approach, as
182 conferred by transseptal access through the catheter “entrapment” within the interatrial septum, may
183 result in improved catheter stability and optimal contact on the mitral annulus, leading to a more
184 effective radiofrequency delivery towards the left sided AP. Failure of an ablation attempt is in fact
185 usually related to a suboptimal catheter stability and catheter-tissue contact during ablation. Of note,
186 the only randomized trial included in the analysis, limited by the very small case sample (only 22
187 patients), did not find any difference between the two approaches [32].

188 Concerning recurrence of conduction over the AP, the incidence was limited between both groups,
189 without significant difference. In fact, the mechanism leading to recurrence is related to a transient
190 effect provided by suboptimal site of ablation, along with the oedema generated by the energy
191 delivery [38]. The majority of difficulties for obtaining good stability through the transaortic
192 approach seem therefore to impair acute efficacy, while the incidence of recurrences, although rare,
193 occurs similarly with both approaches.

194 The overall incidence of complications did not differ between the two groups. It should be noted
195 that pattern of complication is different, as transaortic approach was affected by a significantly
196 higher incidence of vascular complications, while pericardial effusion was the most common
197 complication following transseptal approach (although not reaching statistical significance, see
198 Suppl Table 2). However, transseptal puncture needs specific training, and some Electrophysiology
199 labs are not trained for this approach and therefore mandatorily manage left sided AP by transaortic
200 approach. Of note, the number of transseptal access publications increased during recent years: this
201 trend probably relates to the spread of left atrial ablation for atrial fibrillation, which increasingly
202 favours the comfort level for transseptal puncture. However, in the absence of specific training,
203 transseptal access may provide additional risk; therefore, the results of this analysis should not be
204 generalized to all Electrophysiology Centres.

205 Of note, the overall incidence of complications did not differ compared to the incidence reported for
206 other left-sided arrhythmias ablation approached by transseptal access [39]. Additionally, also
207 vascular complications were comparable to those reported by other electrophysiological procedures
208 [39], although higher than those reported by coronary artery interventional procedures, probably
209 related to the need of anticoagulation during the procedure. Conversely, thromboembolic events did
210 not differ between the two approaches, highlighting that this is not an access-related complication.

211 The meta-regression analysis, performed to assess the impact of the available knowledge and
212 technologies on the outcome of accessory pathway ablation, showed no significant relation between
213 acute efficacy or complications and year of publication. This finding suggests that left sided AP
214 ablation can be safely and effectively performed even using conventional diagnostic and ablation
215 catheters. In fact, although being related to reduction of radiological exposure for patients and
216 physicians (40), the impact on the outcome of AP ablation seems not to be relevant, as previously
217 reported concerning atrial fibrillation ablation. Of note, the overall procedural duration and the
218 fluoroscopy time did not differ between the two approaches. Due to the different tools and

219 technologies, both approaches reported a wide range of both procedural duration and radiological
220 exposure, which appear shorter in the most recent publications. However, decreasing procedural
221 and fluoroscopy durations were parallel between the two approaches, demonstrating that both
222 access types benefit from technological improvements in terms of global simplification and
223 shortening of the procedure, but not in terms of safety or efficacy.

224 Finally, age was not related to different outcome, in terms of both safety and efficacy. This finding
225 emphasizes that left sided AP ablation can be safely performed even in children, in case of clear
226 indication to perform catheter ablation, such as in case of symptomatic, high anterograde
227 conduction APs.

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229 **Limitations**

230 The present analysis includes a large and heterogeneous group of single Centre, observational
231 studies: although heterogeneity was appraised by random effect, the inclusion of non-randomized,
232 retrospective studies may limit the reproducibility of the results. Although excluding case samples
233 and very small series, the experience of each single Centre in performing transcatheter ablation
234 procedures or even left chambers access, including individual operators' comfort level with both the
235 approaches, may have affected the access choice and the outcome of each single study results.
236 Additionally, publication bias cannot be excluded, as a more favourable outcome would have driven
237 the potential interest for publication of these series, compared to other single-Centres series that did
238 never reach publication. However, it should be noted that parameters as year of publication, or age
239 of the included patients, did not affect safety or efficacy of the ablation procedure. Finally, meta-
240 regression analysis does not allow clinicians to drive causative inferences, but only speculative.

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242

243 **Conclusion**

244 Left sided AP transcatheter ablation is effective in around 95% of the patients in trained operators
245 hands, and can be performed with a very limited incidence of complications even in younger
246 patients, when indicated. Transseptal access provides a higher acute success in achieving left sided
247 AP ablation, while late recurrences are limited, but occur similarly following both approaches.
248 While procedural duration and fluoroscopy use are similar, retrograde approach is affected by a
249 relatively higher incidence of vascular complications.

250

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252 The Authors received no external funding for performing this study.

253

254 **Conflicts of interest**

255 The authors report no relationships that could be construed as a conflict of interest.

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258 **Figure legends**

259 **Figure 1.** Acute success (A; 2030 patients from 29 studies) and incidence of recurrences (B; 1338
260 patients from 23 studies) following left-sided accessory pathways ablation.

261 **Figure 2.** Complications of left-sided accessory pathways ablation (1750 patients from 23 studies),
262 procedural duration (1238 patients from 22 studies) and fluoroscopy times (1108 patients from 18
263 studies) of left-sided accessory pathways transcatheter ablation procedures.

264

265 **Table 1.** Pooled clinical features of included studies (2030 patients, 29 studies).

	Transseptal approach (1017 patients)	Transaortic approach (1013 patients)	p-value
Age, years (IQR)	27.8 (17.9-37.6)	34.5 (30.1-39.0)	0.10
Males, % (IQR)	67 (62-72)	67 (59-65)	0.90
Concealed accessory pathways, % (IQR)	34 (20-48)	31 (8-59)	0.76
Site of accessory pathway, % (IQR):			
- Left anterolateral (%)	7 (0.0-15)	7 (2-11)	0.68
- Left lateral (%)	54 (36-70)	67 (57-76)	0.08
- Left posterior (%)	32 (20-44)	12 (4-21)	0.02
- Left posteroseptal (%)	7 (3-12)	14 (7-21)	0.60
Symptoms, % (IQR):			
- AVRT (%)	82 (38-100)	86 (76-95)	0.81
- AF (%)	13 (8-20)	31 (15-51)	0.05
Acute success, % (IQR)	98 (96-100)	94 (90-97)	0.02
Number of RF/Cryo applications, n (IQR)	6.7 (4.6-8.6)	6.1 (4.2-8.0)	0.63
Procedural duration, min (IQR)	179.0 (139.7-218.3)	145.5 (109.2-181.8)	0.23
Fluoroscopy time, min (IQR)	32.2 (19.0-45.3)	32.9 (22.7-43.1)	0.98
Complications, % (IQR)	0.4 (0.0-1.2)	1.2 (0.3-2.6)	0.30
Follow-up duration, months (IQR)	14.5 (10.8-18.1)	12.75 (9.4-16.1)	0.62
Recurrences, % (IQR)	3.2 (1.6-6.1)	2.3 (0.5-4.6)	0.31

266 AVRT: atrioventricular re-entrant tachycardia; AF: atrial fibrillation; RF: radiofrequency; Cryo:
267 cryoablation; IQR: interquartile range.

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271 **Table 2.** Complication pattern reported by transseptal and retrograde transaortic approach

	Transseptal approach (1017 patients)	Transaortic approach (1013 patients)	p-value
Vascular complications (hematoma, pseudoaneurysm)	0	8	0.03
Cardiac tamponade	6	3	0.51
Stroke/TIA	2	1	1.00
Death	0	0	1.00
Peripheral embolism	0	3	0.12
Coronary artery dissection/infarction	1	3	0.37
Mitral regurgitation	1	2	0.62
Aortic regurgitation	0	4	0.06
Aortic dissection	0	1	1.00

272 TIA: transient ischemic attack.

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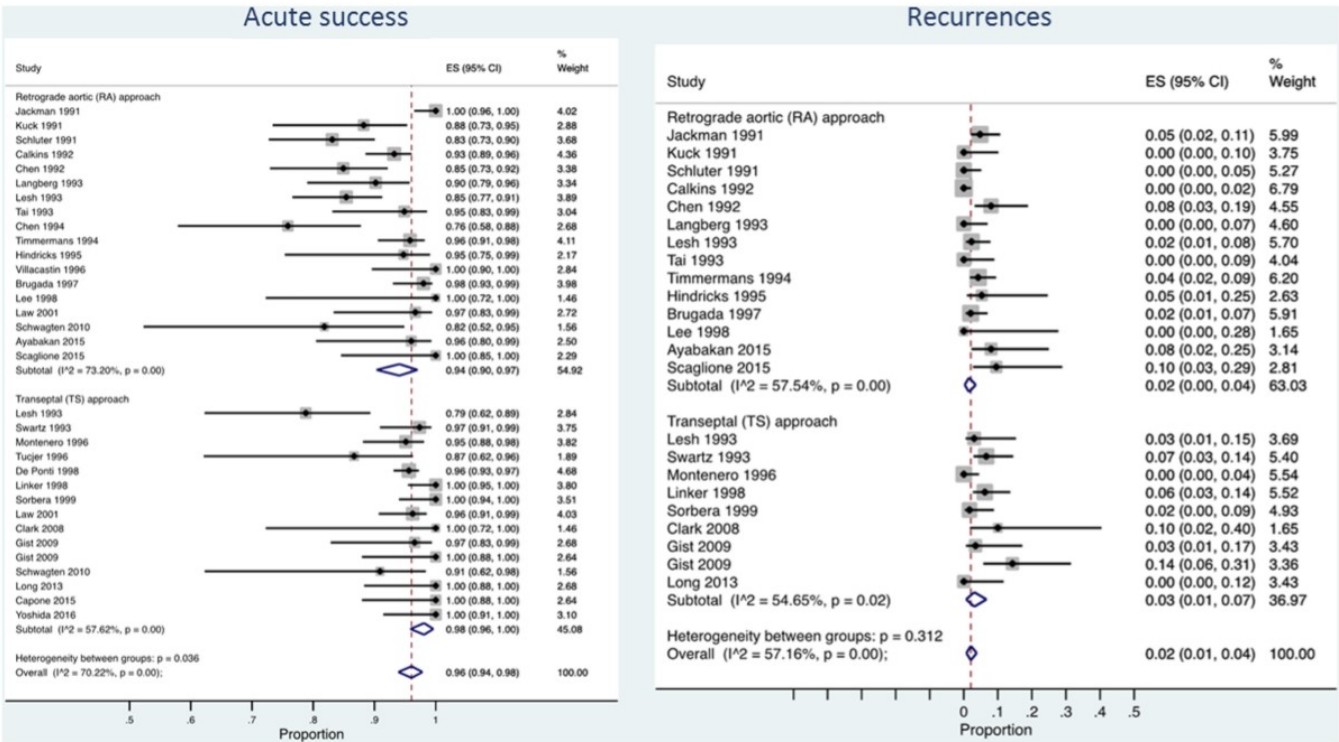
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440 **Figure 1.**



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443 **Figure 2.**

